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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,795	08/29/2003	Brenda F. Baker	ISPH-0768	3627

7590 06/29/2006

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/652,795	BAKER ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *16 Jan 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application is a continuation-in-part of U.S. application Ser. No. 09/824,322, filed Apr. 2, 2001, which is a continuation-in part of allowed U.S. application Ser. No. 09/313,932, filed May 18, 1999 (U.S. Pat. No. 6,228,642), which is a continuation-in-part of U.S. application Ser. No. 09/166,186 filed Oct. 5, 1998 (U.S. Pat. No. 6,080,580).

This priority statement from the specification should be updated to include the status of U.S. application Ser. No. 09/824,322, which is now abandoned. Furthermore, said statement should also be amended to include the date of issue for each U. S. Patent Number.

Although the instant application claims priority via continuation-in-part to earlier applications, all claims are accorded a priority date equivalent to the instant filing date of the present application (i.e. 29 August 2003) since the instant claims are drawn to double stranded RNAs, and since the instant application is the first in the line of priority to teach the use of double stranded oligonucleotides. Should applicants, disagree, applicants are requested to point out with specificity by page and line number where such support may exist in a previous application.

Claim Objections

Claim 6 is objected to because of the following informalities: it appears the word "boackbone" is a misspelling of the word "backbone". Appropriate correction is required.

Claim 1 is objected to because of the following informalities: the opening phrase of said claim recites "An double stranded RNA", which is not grammatically correct. Amendment to recite "A double stranded RNA" would be corrective.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, and by dependency claims 2-7, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed invention is drawn to a "double stranded RNA compound between 8 and 80 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of survivin."

It is unclear how a double stranded RNA compound could specifically hybridize with a nucleic acid molecule encoding human TNF-α, since the double stranded RNA compound is self complementary, and all structures on the double stranded RNA compound which might provide for hybridization with the target are thus already engaged in hydrogen bonding. Clarification is required.

Claim 6 recites the limitation "said amide-containing backbone" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, and by dependency claims 2-7, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a "double stranded RNA compound between 8 and 80 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of survivin."

Neither the instant specification nor the prior art provide adequate description of a method of using a double stranded RNA molecule that hybridizes to a molecule encoding TNF-α, but inhibits the expression of the otherwise unrelated target "survivin". Both the instant specification and prior art are silent as to any relationship between the hybridization of oligos to TNF-α and their effect upon survivin, and it is presumed therefore that the term "survivin" was accidentally inserted in place of " TNF-α ". Such is presumed for the remainder of the instant action.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a double stranded RNA compound that has its sugar backbone replaced with an amide-containing backbone, which may be an aminoethylglycine backbone, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of TNF-α.

The specification teaches single stranded antisense-mediated mRNA inhibition, and teaches that "[w]hile the preferred form of antisense compound is a single-stranded antisense oligonucleotide, in many species the introduction of double-stranded structures, such as double-stranded RNA (dsRNA) molecules, has been shown to induce potent and specific antisense-mediated reduction of the function of a gene or its associated gene products." The specification generically teaches that oligomer mimetics are contemplated, and that PNA (i.e. aminoethylglycine) modifications "have excellent hybridization properties". The specification does not exemplify the use of the claimed fully PNA substituted dsRNA. The prior art is silent as to the use of PNA substituted dsRNA oligomers in gene inhibition.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all

its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

The teachings of the specification in regards to the use of fully substituted PNA dsRNA's are considered to be prophetic, since no examples are actually provided. As stated above, the prior art is silent as to the use of such molecules as well. The instant specification is considered to lack adequate support for the use of fully substituted PNA dsRNA's that have the function of specifically hybridizing with and inhibiting the expression of TNF alpha, since the genus of such molecules is considered to be very large, and unpredictable in view of the fact that the art is silent as to the use of such molecules in target inhibition. In fact, the art teaches that while dsRNA's are effective inhibitors of their cognate target, the use of modifications in such molecules must be done with great care so as to not abolish the activity of such molecules. For example Elbashir et al.(EMBO J. 2001 v20(23)6877-6888) teach that substitution of one or both strands with either 2'- deoxy or 2'-O-methyl modifications effectively abolishes siRNA activity. Since there is very little art which teaches what modifications are tolerated and in what positions

such modifications are tolerated, and since there is no apparent art that teaches how to use the specifically claimed PNA modifications, and since the specification does not cure this defect of teaching how to use fully substituted PNA dsRNA's to inhibit TNF alpha, the specification is considered to lack adequate support in providing a nexus between structures of PNA dsRNA is that have the function of inhibiting TNF alpha.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Sorensen et al. (J. Mol. Biol. 2003, 327(4)761-766.

The instant invention is drawn to a double stranded RNA compound between about 8 and 80 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of survivin (which for reasons discussed above, is interpreted here as TNF-α), wherein said compound comprises between about 12 and 50 nucleobases or 15 and 30 nucleobases in length.

Sorensen et al. teaches a double stranded RNA compound 21-23 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound inhibits the expression of TNF-α.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U. S. Patent Number 6,228,642), and further in view of Vickers et al. (J. Biol. Chem. 2003, 278(28)7108-7118.).

Although the instant application claims priority to the patent of Baker et al., priority has been denied for reasons provided above under the heading "Priority".

The instant invention is drawn to a double stranded RNA compound between about 8 and 80 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of survivin (which for reasons discussed above, is interpreted here as TNF-α), wherein said compound comprises between about 12 and 50 nucleobases or 15 and 30 nucleobases in length. The invention is also drawn to the compound of claim 1, wherein said compound comprises SEQ ID NO:432.

Baker et al. teach antisense oligonucleotides comprising SEQ ID NO: 432.

Vickers et al. teaches a comparative study of optimized antisense oligonucleotides designed to work through an RNAi mechanism to those designed to work by an RNase H

dependent mechanism. Vickers concludes that the potency, maximal effectiveness, duration of action, and sequence specificity of antisense and siRNA oligos are comparable.

It would have been obvious to one of ordinary skill in the art to use the antisense oligonucleotide of Baker et al. comprising SEQ ID NO: 432 in the formulation of an siRNA oligonucleotide targeting TNF alpha. One of ordinary skill would of been motivated to convert the antisense oligonucleotide of SEQ ID NO: 432 into an siRNA oligonucleotide, since Vickers et al. teaches that RNA interference has become a powerful and widely used tool for the analysis of gene function, and since SEQ ID NO: 432 has already been shown to provide effective antisense oligonucleotide-based inhibition of TNF alpha.

Since Baker et al. teach the full sequence of SEQ ID NO: 432, and since Vickers et al. teach that siRNA oligonucleotides are simply double stranded versions of their antisense precursors, one of ordinary skill in the art would have had a reasonable expectation of success in making such oligonucleotides. Accordingly, the invention would have been considered considered prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 and 7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of Baker et al. (U. S. Patent Number 6,228,642) in view of Vickers et al. (J. Biol. Chem. 2003, 278(28)7108-7118.).

The instant invention is drawn to a double stranded RNA compound between about 8 and 80 nucleobases in length targeted to a nucleic acid molecule encoding human TNF-α, wherein said compound specifically hybridizes with said nucleic acid molecule encoding TNF-α and inhibits the expression of survivin (which for reasons discussed above, is interpreted here as TNF-α), wherein said compound comprises between about 12 and 50 nucleobases or 15 and 30 nucleobases in length. The invention is also drawn to the compound of claim 1, wherein said compound comprises SEQ ID NO:432.

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Vickers et al. teaches a comparative study of optimized antisense oligonucleotides designed to work through an RNA I've mechanism to those designed to work by an RNase H dependent mechanism. Vickers concludes that the potency, maximal effectiveness, duration of action, and sequence specificity of antisense and siRNA oligos are comparable.

It would have been obvious to one of ordinary skill in the art to use the antisense oligonucleotide of Baker et al. comprising SEQ ID NO: 432 in the formulation of and siRNA

oligonucleotide targeting TNF alpha. One of ordinary skill would of been motivated to convert the antisense oligonucleotide of SEQ ID NO: 432 into and siRNA oligonucleotide, since Vickers et al. teaches that RNA interference has become a powerful and widely used tool for the analysis of gene function, and since SEQ ID NO: 432 as Artie been shown to provide effective antisense oligonucleotide based inhibition of TNF alpha.

Since Baker et al. teach the full sequence of SEQ ID NO: 432, and since Vickers et al. teach that siRNA oligonucleotides are simply double stranded versions of their antisense precursors, one of ordinary skill in the art would have had a reasonable expectation of success in making such oligonucleotides. Accordingly, the invention would have been considered considered prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER